

Introduction

Influenza Vaccine

Session

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Advisory Committee on Immunization Practices

February 21, 2007

Agenda: Influenza Session

- Status of influenza activity in the US (*Anthony Fiore, CDC*)
- Status of antiviral drug resistance (*Fiore*)
- Update on projected influenza vaccine supply (*Fiore*)
- Highlights of the 2007 influenza vaccine recommendations (*Fiore*)
 - Recommendations vote
- VFC vote (*Greg Wallace, CDC*)
- Interagency pandemic vaccine prioritization workgroup update (*Ben Schwartz, NVPO*)
- Safety and efficacy of cold-adapted influenza vaccine (CAIV-T) in children < 5 years old (*Robert Walker, MedImmune*)

Progress in Influenza Prevention Efforts

- **Epidemiology**
 - Better, more timely population-based data
- **Vaccine Effectiveness**
 - More data based on lab-confirmed infection, larger studies
 - Critical questions being addressed (e.g., 2 doses for young children)
- **Vaccine Coverage**
 - Improving among infants and toddlers
 - Rebounding among elderly and adults after vaccine shortage season of 2004-2005
- **Manufacturing Capacity**
 - Expanding, increased availability of preservative free formulations
 - New formulations in pipeline
- **Immunization programs**
 - Improved flexibility and innovative settings

Continuing Challenges

- Low coverage in some groups at high risk of complications
- Vaccine immunogenicity/effectiveness not optimized
- Effectiveness and safety studies needed yearly
- Implementation of vaccination programs is difficult
 - flexibility in scheduling and capacity
 - supply delays or shortages
 - unpredictable public demand
 - communication messages

Milestones in Recommendation Changes

2000: All adults 50 and older

2004: All children aged 6--23 months
All women who will be pregnant during influenza season

2005: All persons with any condition that can compromise respiratory function or the handling of respiratory secretions

2006: All children aged 24--59 months and their household contacts and out-of-home caregivers

Criteria for Changing Vaccination Recommendations

- Safety
- Effectiveness
 - Morbidity/mortality
 - Hospitalizations
 - Outpatient and emergency department visits
- Indirect effects (preventing illness among contacts)
- Feasibility of implementation
- Cost-effectiveness
- Vaccine supply

Considerations for Expanding Recommendations to Include Routine Vaccination of all Children 6 Years or Older

- Many older children are already recommended for annual vaccination: household contacts of younger children, persons at high risk, or elderly
- Routine influenza vaccination of older (5-18 year old) children
 - Would reduce morbidity and mortality among children
 - Might reduce community-wide morbidity and mortality by indirect effects
 - Creates expectation of immediate implementation of immunization programs for this age group that might be difficult to meet
 - Might exacerbate vaccine supply shortages and distribution delays if lead time for planning is insufficient
- Planning for recommendation expansion requires input from epidemiologists, immunologists, vaccine safety experts, immunization program managers, communications experts, manufacturers, economists, education officials, funding entities, and the general public

Potential Time-Frame for Modifying Influenza Vaccination Recommendations

- **2007-2008:** Consider expanding recommendations to include all school-age children (6 months-18 years): Summarize evidence and address critical issues
 - Organize meeting to consider scientific and implementation issues
 - Summarize results for the October 2007 ACIP meeting
 - If recommendations are changed
 - Assist manufacturers, immunization programs, and public health communication experts in planning implementation for 2008-2009 influenza season
- **2010-2011:** Possible expansion of recommendations to include household contacts and caregivers of school-aged children.
- **2012-2013:** Possible expansion to universal vaccination (extend recommendations to persons 18-49 years).

Influenza Activity in the United States, February 2007*

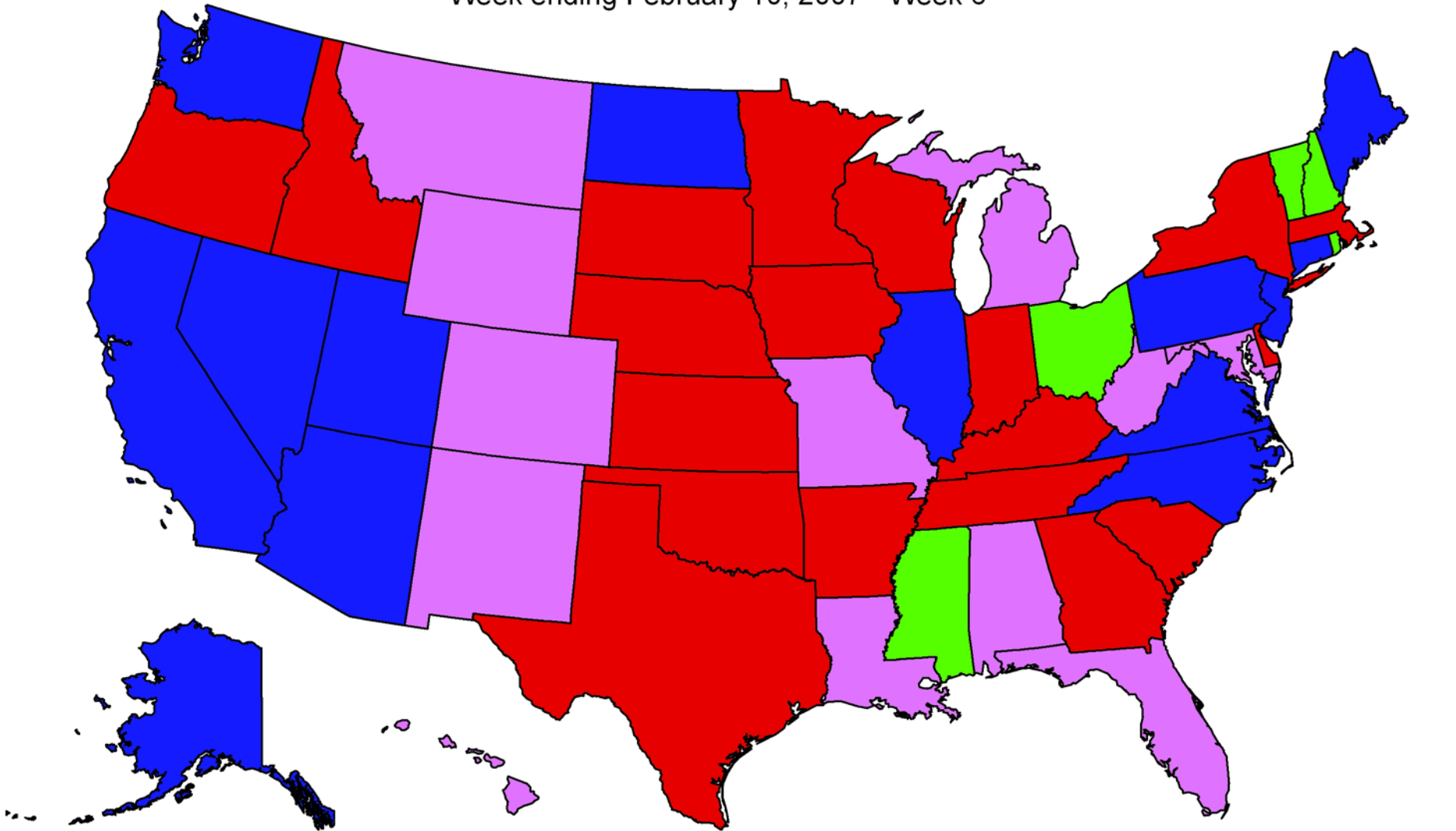
Anthony Fiore, MD

***Influenza Division, CDC Preliminary data**



Weekly Influenza Activity Estimates Reported by State & Territorial Epidemiologists

Week ending February 10, 2007 - Week 6



No Report



No Activity



Sporadic



Local Activity



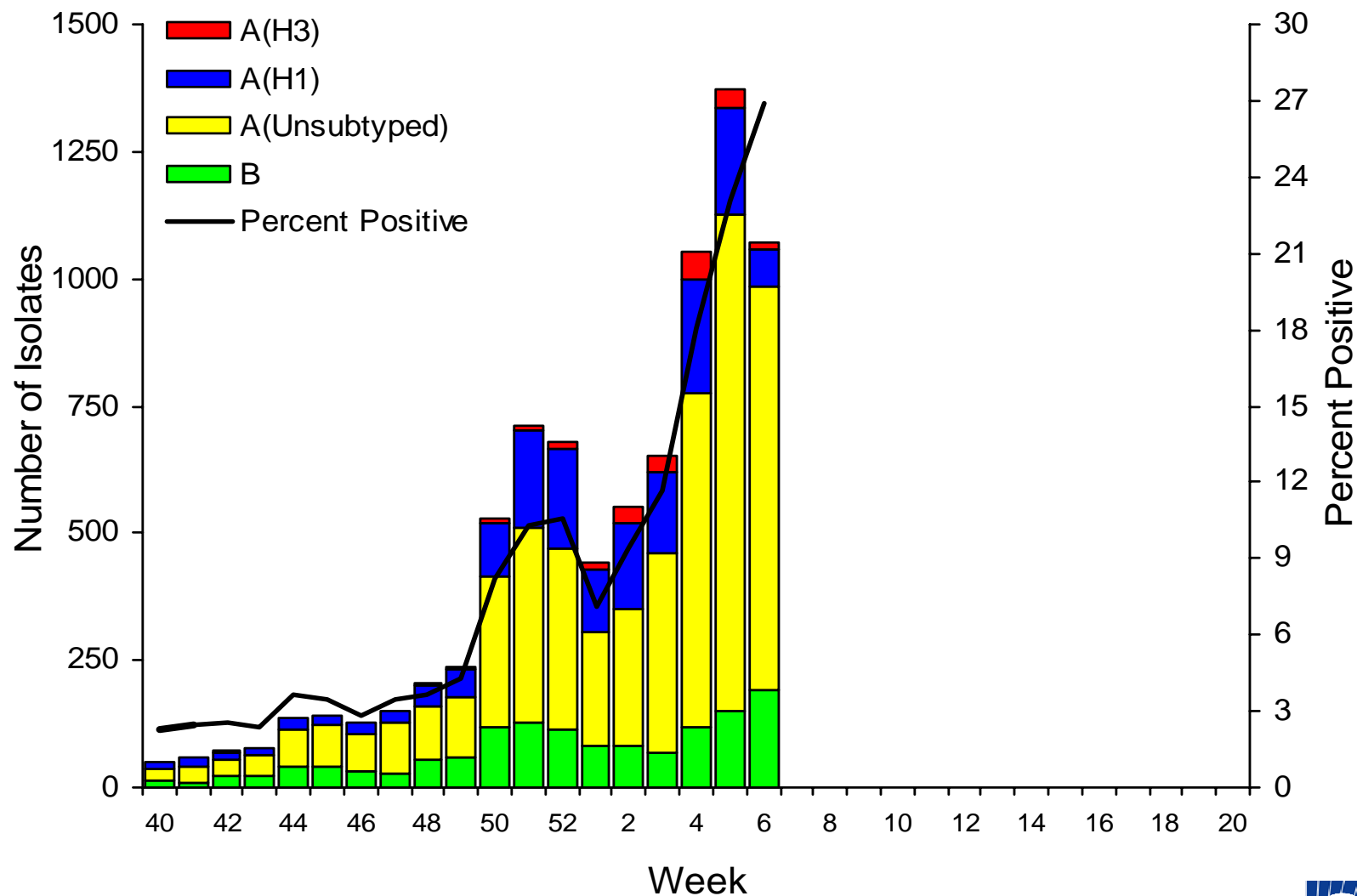
Regional



Widespread



U.S. WHO/NREVSS Collaborating Laboratories Summary, 2006-07



Strain Characterization, 2006-7 Season

CDC has characterized 161 viruses through February 10

Influenza A (H1N1) [n=99]:

- 93 (94%) similar to A/New Caledonia/20/99-like viruses
- 6 (6%) with reduced titers to A/New Caledonia

Influenza A (H3N2) [n=7]

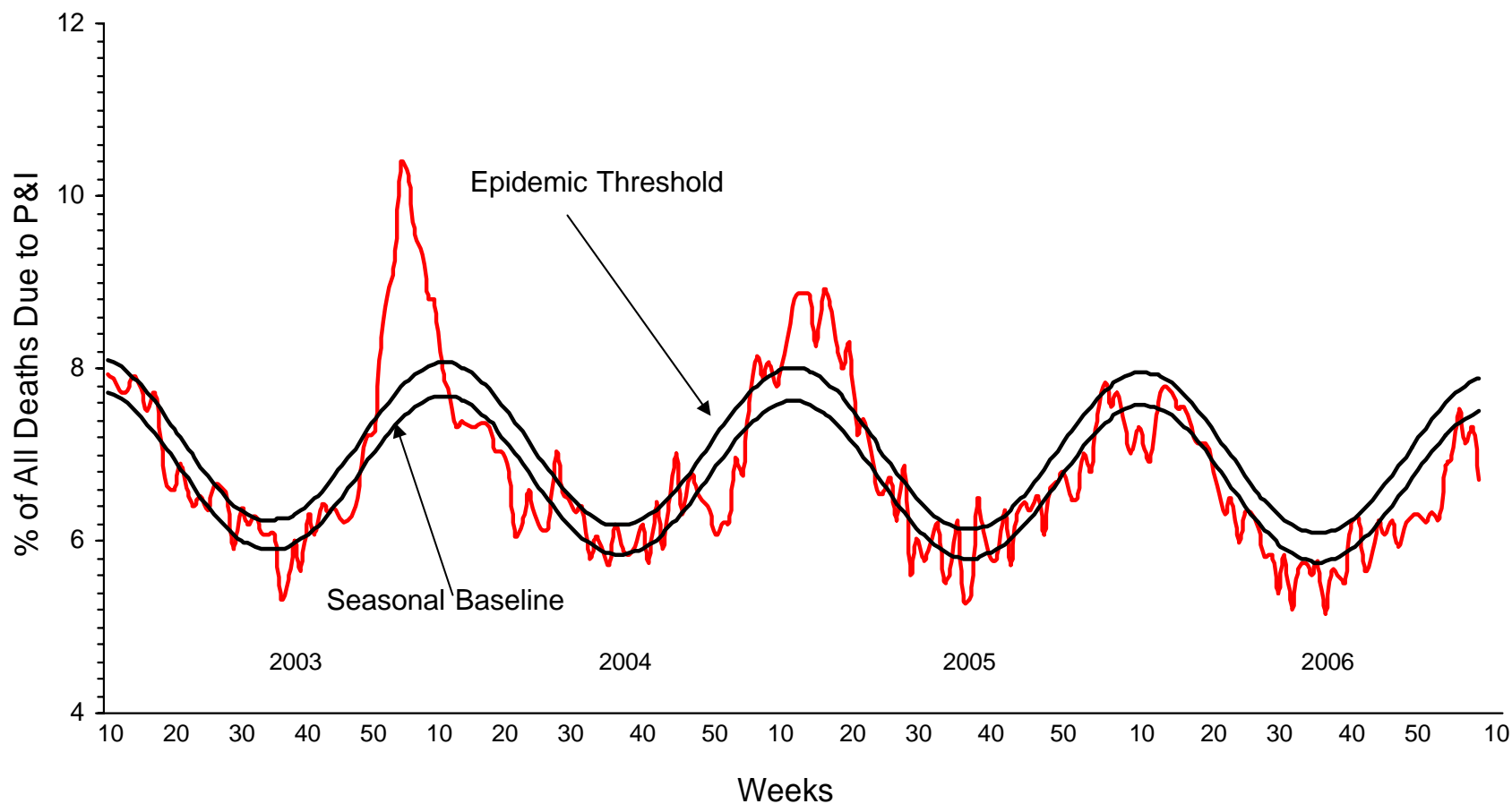
- Four similar to A/Wisconsin/67/2005-like viruses
- Three with reduced titers to A/Wisconsin/67/2005

Influenza B [n=55]

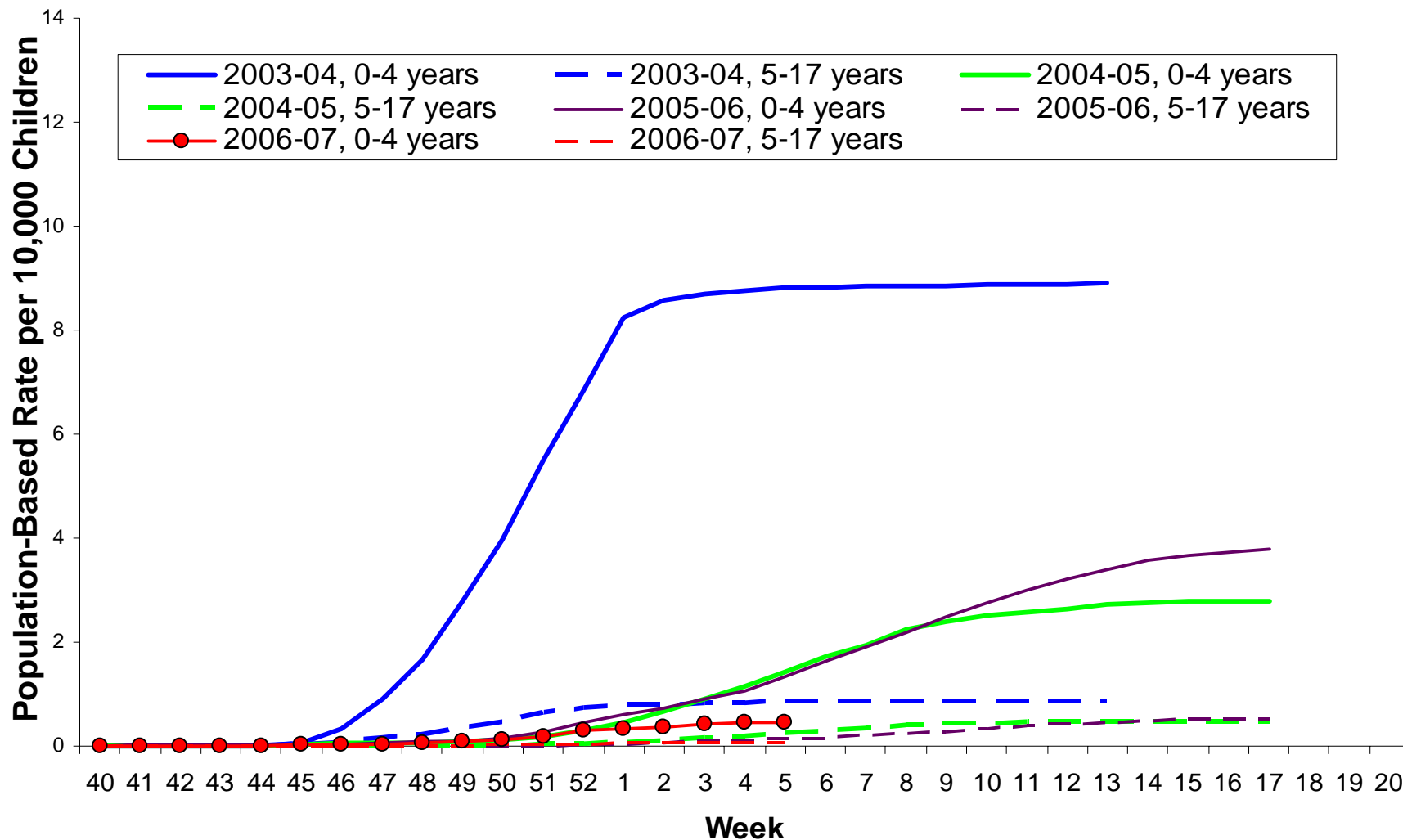
- 67% in B/Victoria lineage
 - 49% similar to B/Ohio/01/2005
 - 51% somewhat reduced titers to B/Ohio
- 33% in Yamagata lineage

Pneumonia and Influenza Mortality for 122 U.S. Cities

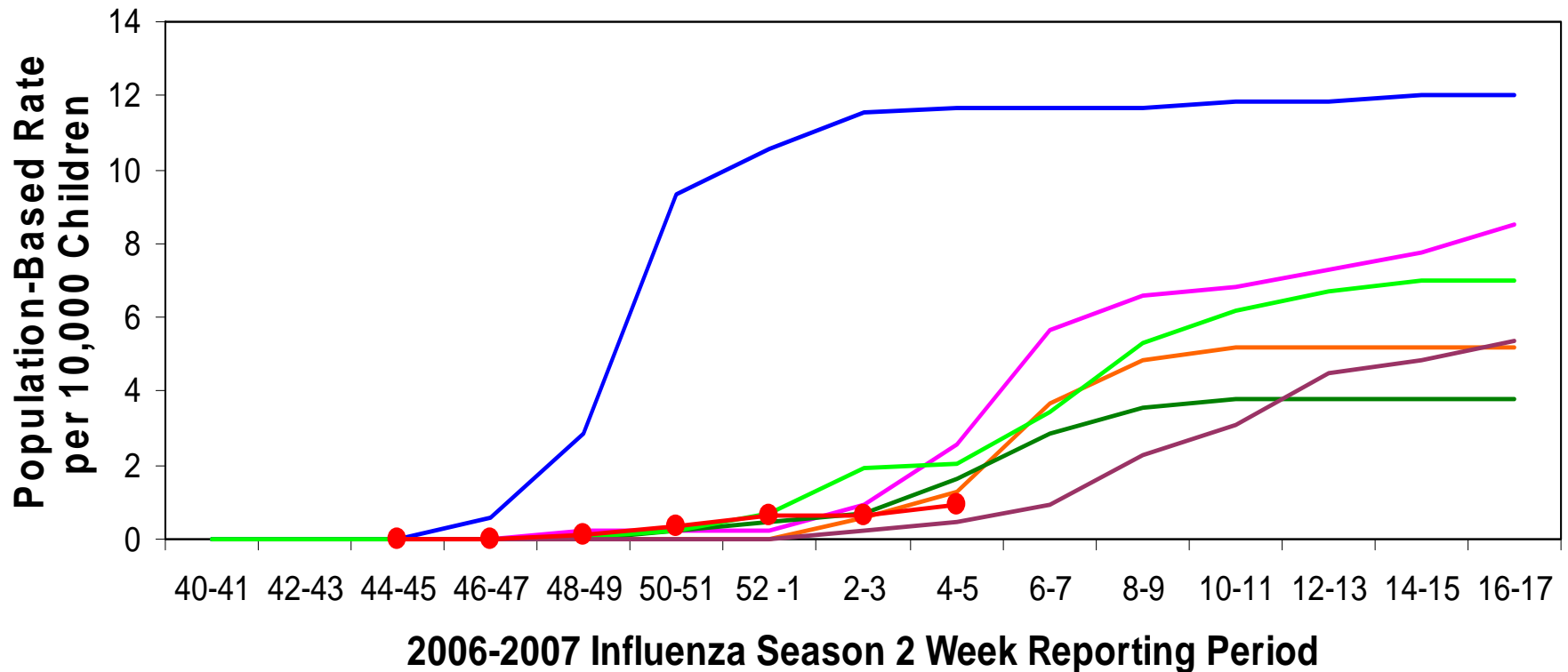
Week Ending 02/10/2007



Emerging Infections Program: Cumulative Hospitalization Rates for Laboratory-Confirmed Influenza Children Aged 0-4 and 5-17 years, 2006-07 and Previous 3 Seasons



New Vaccine Surveillance Network: Cumulative Hospitalization Rates for Laboratory-Confirmed Influenza among Children 0 - 4 Years, 2006-07 and Previous 6 Seasons



— 2000-2001 — 2001-2002 — 2002-2003 — 2003-2004 — 2004-2005 — 2005-2006 ● 2006-2007

Surveillance for Pediatric Deaths Attributed to Influenza Complications

- As of February 15, 2007, CDC has received 15 reports of influenza-associated pediatric deaths this season
 - 10 were 5 years of age or older
 - Underlying medical conditions
 - 3 with underlying conditions that might have contributed to severity
 - 5 with no known underlying conditions
 - 2 with unknown previous health status
 - 4 had MRSA bacteremia
 - Vaccination status
 - Unvaccinated (9)
 - Vaccinated (1)
- 2004-2005: 44 deaths
- 2005-2006: 48 deaths
- 2003-2004: 153 deaths

Antiviral drug resistance during the 2006-2007 influenza season (preliminary)

Resistance to Adamantanes (amantadine and rimantadine)

- Rapid emergence of resistance identified during 2005*
 - **H1N1** : 2 of 8 (25%) adamantane-resistant
 - **H3N2** : 192 of 209 (92%) adamantane-resistant
- Fewer adamantane-resistant isolates in 2006-2007**
 - Global surveillance
 - H1N1: 5 of 199 (3%)
 - H3N2: 24 of 54 (44%)
 - U.S. isolates
 - H1N1: 1 of 91 (1%)
 - H3N2: 3 of 10 (33%)

* Bright et al. (2006): JAMA 295; 891-4

** L Gubareva, CDC, preliminary data

Resistance to Neuraminidase Inhibitors (oseltamivir and zanamivir)

- Neuraminidase inhibitor-resistant human influenza viruses rare ($<0.5\%$)*
- No resistance to oseltamivir or zanamivir among isolates tested at CDC since 2005 ($n=437$)**

* Monto et al. (2006): Antimicrob Ag Chemother 50; 2395-2402

** L Gubareva, CDC, preliminary data

**Projected Capacity for Influenza
Vaccine Production:
Manufacturer's Update**

Projected Influenza Vaccine Supply, TIV (GSK)

- 2007-8
 - ~35-40 million doses adult vaccine (10 million more than 2006-2007 season)
 - ~1/3 from Dresden facility (Fluarix, trace thimerosal, single dose)
 - ~2/3 million from Canada facility (Flulaval, thimerosal preservative, multidose)
- Currently conducting studies of pediatric vaccine (trace thimerosal)
- Pediatric vaccine (thimerosal-free) under development

Projected Influenza Vaccine Supply (MedImmune, LAIV/CAIV-T, thimerosal free)

- 2007-8: ~ 7 million doses FluMist for 5-49 year olds (pending licensure for 1-49 year olds)
- Next 3-5 years
 - 2008-2009: ~20 million doses FluMist
 - 2009-2013: ~35-90 million doses FluMist

Projected Influenza Vaccine Supply (Novartis)

- 2007-8
 - Up to 40 million doses
- Next 3-5 years
 - Up to 45 million doses per year
 - Planning to shift most production to preservative free
- Expanding its influenza capacity with the development of cell culture based influenza vaccine
 - Possibility of limited quantities in 2008
 - Up to 50 million doses of cell based influenza vaccine by 2012
 - A significant percentage of the cell based vaccine will be supplied in a preservative free presentation

Projected Influenza Vaccine Supply (sanofi/pasteur)

No new information provided for February 2007 ACIP meeting

Statement provided at October 2006 ACIP meeting:

“A new enclosed facility is under construction that will double sanofi pasteur’s capacity in 2008-2009 and allow for production of 100 million doses of influenza vaccine. In 2007 or 2008, sanofi pasteur expects to build a new fill and formulation facility that would allow for an expansion over the current 8-9 million doses of preservative-free vaccine.”

Projected Overall Capacity

- 2007-2008:
 - ~130 million doses might be available for 2007-2008 season
 - ~20 million preservative free doses
 - Only 1 manufacturer currently licensed to supply preservative-free TIV for children
 - LAIV is thimerosal-free
- Next 3-5 years:
 - 150-200 million doses possible
 - Increased preservative-free capacity expected
- All estimates contingent on growth characteristics of vaccine strains, manufacturing and licensure constraints, and market demand

Prevention and Control of Influenza during the 2007-2008 Influenza Season

Recommendations of the Advisory
Committee on Immunization Practices
(ACIP)

Key Issues, 2007 Recommendations

- Changes to vaccine composition
 - Will be decided at VRBPAC meeting Feb 28, 2007
- Continue to recommend against the use of adamantanes
 - >30% resistance among H3N1 strains in U.S. this season
- Change in recommendations for children ages 6 months to <9 years who received a single dose during their first (previous) year of vaccination
 - **New:** recommended to receive 2 doses in second year of vaccination
- Age groups and risk groups for whom routine vaccination is recommended is not changed compared to 2006 recommendations

Reorganization

- Summary
- Box – recommendations
- Methods
- Background and Epidemiology
- Vaccine Efficacy, Effectiveness and Safety
 - TIV and LAIV in separate subsections
 - TIV vs. LAIV comparison studies
- Recommendations for Using Vaccine
- Recommendations for Vaccine Administration and Immunization Programs
- Antivirals

Recommendations Box – Slide 1

Vaccination is recommended for persons, including school-age children, who want to reduce the likelihood of becoming ill with influenza or transmitting influenza to others should they become infected. Healthy, nonpregnant persons who are 5 through 49 years old can choose to receive either trivalent inactivated influenza vaccine (TIV) or live attenuated influenza vaccine (LAIV; also referred in some literature as cold-adapted influenza vaccine, trivalent [CAIV-T]). All others should receive TIV.

Recommendations Box – Slide 2

All persons in the following groups should receive annual influenza vaccination. Vaccination efforts should focus on delivering vaccination to these persons if vaccine supply is limited:

- All children aged 6–59 months (i.e., 6 months to <5 years of age);
- All persons aged ≥ 50 years;
- Healthy household contacts (including children) and caregivers of infants who are younger than 6 months old
- Children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza virus infection;
- Women who will be pregnant during the influenza season;
- Adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological or metabolic disorders (including diabetes mellitus);
- Adults and children who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; and
- Residents of nursing homes and other chronic-care facilities.

Recommendations Box – Slide 3

In addition, to prevent transmission to persons such as those identified above, all persons in the following groups should receive annual influenza vaccination with TIV or LAIV unless contraindicated:

- Health care workers;
- Healthy household contacts (including children) and caregivers of children 0-59 months of age and adults >50 years of age; and,
- Healthy household contacts (including children) and caregivers of persons with medical conditions (see above) that put them at higher risk for severe complications from influenza.

Children ages 6 months to <9 years who received only 1 dose in their first year of vaccination: 2006 recommendations

- All children ages 6 months to <9 years being vaccinated for the first time should get two doses
 - Some only get 1 dose in the first season of being vaccinated
- 2006 recommendation: children aged 6 months to <9 years who received an influenza vaccine for the first time in the previous season but who did not receive the recommended second dose of vaccine within that first season need only receive 1 dose in the second season

Evidence supporting use of 2 doses in second year of vaccination for children ages 6 months to <9 years who received only 1 dose in their first year of vaccination

- *Englund* et al, Pediatrics 2006: When the influenza B antigen was changed for the second season, children who only received 1 dose in their first season of being vaccinated and 1 dose in second season had decreased immunologic response to the influenza B antigen compared to children who received 2 doses
- *Allison* et al J Pediatr 2006: In consecutive seasons when the influenza vaccine antigens were unchanged, effectiveness against ILI in second season was significantly less for 6-21 month old children being vaccinated for the first time who received 1 dose in both seasons compared to 6-21 month old children in their first season who received 1 dose in first season and 2 doses in second season

**Children ages 6 months to <9 years who received
only 1 dose in their first year of vaccination:
2007 recommendations**

New recommendation (2007): “The ACIP now recommends 2 vaccine doses for children aged 6 months to <9 years who received an influenza vaccine for the first time in the previous season but who did not receive the recommended second dose of vaccine within that first season.”

Vaccine safety: thimerosal

“No scientifically conclusive evidence has demonstrated harm from exposure to thimerosal preservative-containing vaccine. Persons recommended to receive TIV may receive any age- and risk factor-appropriate vaccine preparation, depending on availability.”

Emphasizing Need for Better Vaccination Coverage among Health Care Workers

- “All health-care workers, as well as those in training for healthcare professions, should be vaccinated against influenza annually. Facilities that employ health-care workers should provide vaccine to workers by using approaches that maximize vaccination levels. Higher vaccination coverage levels would likely protect health-care workers, their patients, and communities; improve prevention of influenza-associated disease and patient safety; and reduce disease burden. Influenza vaccination rates among health-care workers should be regularly measured and reported.”
- Noted new JCAHO regulations that require accredited organizations to offer vaccination and measure vaccination coverage among staff
- Noted professional organization proposals, and state health law requirements, that healthcare workers be vaccinated or provide a written statement declining vaccination

Additional healthcare worker-related text suggested by reviewers

- Add sentence in summary: “All healthcare workers should be offered vaccination, and those who refuse influenza vaccination for reasons other than medical contraindications should be required to provide a signed declination.”
- Note Healthy People 2010 objective (60% coverage) for HCW immunization
- Reference additional professional society recommendations and state regulations requiring vaccination for HCWs unless they provide written declination

Recommendations for Immunization Programs

Timing of Organized Vaccination Campaigns

“Vaccination clinics should be scheduled through December, and later if feasible, with attention to settings that serve children 6-59 months of age, pregnant women, other persons aged <50 years at increased risk for influenza-related complications, persons aged ≥ 50 years, health-care workers, and household contacts of healthy children aged 24-59 months and persons at high-risk (including children aged 0–23 months) to the extent feasible. Planners are encouraged to develop the capacity and flexibility to schedule at least one vaccination clinic in December.”

Timing of vaccination

“Vaccine should be administered starting in late September and October and should continue through January and beyond because influenza activity typically peaks in February/March in the majority of seasons. Health care providers should be alert to potential vaccination opportunities during all healthcare encounters, including diagnostic or minor surgical procedures. As influenza season approaches, and whenever influenza vaccine is available, office staff should advocate or offer vaccination whenever patients contact medical care facilities, including during requests for services such as prescription refills or appointment requests.”

Recommendations for Using Antivirals

“Amantadine and rimantidine should not be used for the treatment or prevention of influenza in the United States until evidence of susceptibility to these antiviral medications has been re-established among circulating influenza A virus subtypes.”

Discussion and Questions